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## **Lung cancer survival in Switzerland by histology, TNM stage and age at diagnosis**

Galli, Francesco ; Rohrmann, Sabine ; Lorez, Matthias

**Abstract:** In 2017, more than 3 out of 100 deaths worldwide were attributed to lung cancer, making it the deadliest malignancy [1]. In Switzerland, it is the second most frequent cancer among men and the third most frequent among women. Every year, 4,400 individuals are diagnosed with lung cancer and 3,200 die of it [2]. A well-established risk factor is smoking. Indeed, lung cancer risk is on average 5-10 times higher among smokers compared to nonsmokers [3]. The differences in smoking habits between men and women influenced the evolution of lung cancer incidence over the last century. Men started smoking in large numbers already in the early 1900's, while among women smoking became more common later in the century. In recent years, a decrease in incidence and mortality rates in developed countries has been observed among men but not among women [4, 5]. Today lung cancer is still more common among men than among women (incidence ratio 1.8:1) [6]. Despite smoking's major role in lung carcinogenesis, approximately 10-15% of all cases occur in never-smokers. Second-hand smoke, radon gas, air pollution, exposure to occupational agents and genetic predisposition are the main risk factors to which these cases are attributed [7]. Late diagnosis and limited treatment reduce the chances of lung cancer survival. In Europe, lung cancer survival five years after diagnosis was reported to be, on average, lower than 15% [8]. However, a number of factors must be taken into account in order to correctly predict the prognosis of a lung tumour. Survival has been shown to be considerably worse among patients suffering from small cell lung cancer (SCLC) compared to those with non-small cell histology (NSCLC) [9]. Moreover, as for other cancers, the tumour stage at time of diagnosis weighs substantially on the treatment options and their success. Finally, women are known to have a better survival than men and the elderly a worse prognosis compared to younger individuals [10-12]. In the present study, we update our previously published lung cancer survival data [13] for the period 2011-2015 and we extend estimation of survival to ten years after diagnosis. Moreover, we present for the first time survival following lung cancer in Switzerland by histological subgroup, UICC TNM stage and age group.

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# Lung cancer survival in Switzerland by histology, TNM stage and age at diagnosis

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**Keywords:** Lung cancer, Relative Survival, Survival, Switzerland

## Introduction

In 2017, more than 3 out of 100 deaths worldwide were attributed to lung cancer, making it the deadliest malignancy [1]. In Switzerland, it is the second most frequent cancer among men and the third most frequent among women. Every year, 4,400 individuals are diagnosed with lung cancer and 3,200 die of it [2]. A well-established risk factor is smoking. Indeed, lung cancer risk is on average 5-10 times higher among smokers compared to non-smokers [3]. The differences in smoking habits between men and women influenced the evolution of lung cancer incidence over the last century. Men started smoking in large numbers already in the early 1900's, while among women smoking became more common later in the century. In recent years, a decrease in incidence and mortality rates in developed countries has been observed among men but not among women [4, 5]. Today lung cancer is still more common among men than among women (incidence ratio 1.8:1) [6]. Despite smoking's major role in lung carcinogenesis, approximately 10-15% of all cases occur in never-smokers. Second-hand smoke, radon gas, air pollution, exposure to occupational agents and genetic predisposition are the main risk factors to which these cases are attributed [7].

Late diagnosis and limited treatment reduce the chances of lung cancer survival. In Europe, lung cancer survival five years after diagnosis was reported to be, on average, lower than 15% [8]. However, a number of factors must be taken into account in order to correctly predict the prognosis of a lung tumour. Survival has been shown to be considerably worse among patients suffering from small cell lung cancer (SCLC) compared to those with non-small cell histology (NSCLC) [9]. Moreover, as for other cancers, the tumour stage at time of diagnosis weighs substantially on the treatment options and their success. Finally, women are known to have a better survival than men and the elderly a worse prognosis compared to younger individuals [10-12].

In the present study, we update our previously published lung cancer survival data [13] for the period 2011-2015 and we extend estimation of survival to ten years after diagnosis. Moreover, we present for the first time survival following lung cancer in Switzerland by histological subgroup, UICC TNM stage and age group.

## Methods

### *Study population*

Data on lung cancer cases were extracted from the anonymised national cancer dataset managed by the Foundation National Institute of Cancer Epidemiology and Registration (NICER). Data from seven Swiss cancer registries were used for the present study, namely Basel City and Basel Country (BS/BL), Fribourg (FR), Geneva (GE), Ticino (TI), Valais (VS), Vaud (VD) and Zurich (ZH), selected by completeness of registration coverage and of TNM staging information over the analysis period. Registries recorded all incident cancer cases diagnosed in their resident population and assessed cases' survival through 31 December 2015. A small proportion of living cases (6%) had a last available follow-up date before 31 December 2015. The life status of these cases was changed to lost to follow-up. The incidence date refers to the date of confirmation of diagnosis. Completeness of case ascertainment for lung cancer has been determined in all study registries and found to be higher than the international standard of at least 90% within three years after the date of diagnosis [14]. We selected cases with primary malignant lung cancer (C33.9 to C34.9 in ICD-O, 3<sup>rd</sup> edition) [15], aged 30-99 years and diagnosed 1999-2015. For BS/BL, the diagnosis period was 1999-2012 and for FR it was 2006-2015. Lung cancer cases were retained even if preceded by a primary cancer with a different topography [16]. All cases diagnosed at death were excluded. Tumour stage was coded according to the TNM classification of malignant tumours [17]. On average, 23% of the cases did not have enough information to determine tumour stage. The histology codes were grouped into SCLC and NSCLC using the definitions and morphologies described

by Lewis et al. [18]. Tumours other than carcinomas were excluded from the analysis.

### Statistical analysis

Relative survival (RS) probabilities were calculated for consecutive time intervals after diagnosis during which the hazards were assumed to remain constant. Hazards are known to decrease more steeply in the first year after diagnosis; therefore, we defined intervals with increasing length (at 2, 4, 6, 9, 12, 15, 18, 24, 36, 48, 60 and 120 months after diagnosis). RS expresses the ratio of the observed probability of survival of cancer cases and the expected survival of individuals in the general population with same age, sex, calendar year of death and canton. This allows for estimating mortality due to lung cancer by accounting for competing risk of death [19]. Survival estimates were produced using the period approach, which provides more up-to-date values than the traditional cohort approach [20]. In brief, period analysis presents the survival experience of cases selected by a period of vital status follow-up dates, in our case 2011-2015. Age-standardization of RS estimates used weights, as well as the method for calculating 95% confidence intervals (95% CI), as defined by the International Cancer Survival Standard [21]. In the case of age-specific RS (crude RS), 95% CI were estimated by applying the delta method to a transformation of the cumulative hazard [22].

All analyses were performed using the Stata Statistical Software (version 15.1).

### Results

A total of 12,611 cases were included in the analysis. Table 1 displays the contribution of cancer registries to the case pool, as well as the distribution of lung cancer diagnoses by histology, TNM stage and age group.

As can be seen in figure 1, survival of lung cancer patients steeply decreased over the course of the first year following the diagnosis. One-year survival amounted to 59% among women and 50% among men. After the first year post-diagnosis, the sex-specific survival curves ran in parallel and reached a five-year survival probability of 24% in women and of 19% in men. Ten years after the diagnosis, women had a survival of 15% and men of 11%.

Table 2 shows one-, five- and ten-year age-standardized relative survival stratified by histology, TNM stage and age at diagnosis. Survival was consistently higher among women, regardless of the investigated prognostic factor. However, poor prognosis for SCLC patients seems to be equally dramatic for men and women. Indeed, SCLC survival was lower than 50% in both sexes already after the first year and decreased to single digits after five years. TNM stage at diagnosis is a very informative predictor for lung cancer survival: stage I lung cancer patients had

a higher than 90% survival after the first year, while stage IV patients experienced a survival of only 27-37% at the end of the same period. Tumour stage is also the factor according to which survival varied the most between sexes. Finally, larger differences in survival by age group were observed among women, as compared among men, but in both sexes, the highest age group (75 and older) had a lower survival than younger ages.

### Discussion

In this study, we provided up-to-date estimates of survival following lung cancer diagnosis in Switzerland. The reported five-year relative survival rates of 19% in men and 24% in women are substantially higher than the European average (13%) [8], although they are comparable to more recent estimates from neighbouring countries [23, 24] and the United States [25]. Lung cancer prognosis seems to be more favourable compared to previous years [13]: one-year

	Number of cases			% of cases
Overall	Men 7,417	Women 5,194	Total 12,611	100.0
<b>Registry</b>				
BS/BL	558	388	946	7.5
FR	529	348	877	7.0
GE	885	647	1,532	12.1
TI	956	588	1,544	12.2
VD	1,362	970	2,332	18.5
VS	655	438	1,093	8.7
ZH	2,472	1,815	4,287	34.0
<b>Histology</b>				
SCLC	938	710	1,648	13.1
NSCLC	6,479	4,484	10,963	86.9
<b>TNM stage</b>				
I	1,376	1,043	2,419	19.2
II	631	358	989	7.8
III	1,239	784	2,023	16.0
IV	2,514	1,806	4,320	34.3
Missing	1,657	1,203	2,860	22.7
<b>Age group</b>				
30-54	825	759	1,584	12.6
55-64	1,894	1,459	3,353	26.6
65-74	2,716	1,788	4,504	35.7
75+	1,982	1,188	3,170	25.1

Tab. 1. Distribution of cases by cancer registry, tumour histology, TNM stage and age at diagnosis.

survival increased from 42-48% in 2005-2009 to 50-59% in 2011-2015, and five-year survival from 14-18% to 19-24%. Increasing survival trends have also been observed elsewhere in Europe [26] and are likely attributable to the slow, but steady improvement in diagnostic tools and treatment options in the last decades, particularly in the areas of adjuvant therapy following tumour resection and redefinition of therapy options for advanced neoplasms [27]. Furthermore, overall survival may have benefitted from a shift towards tumour histologies with more favourable prognosis. Survival is much higher for the NSCLC subtypes adenocarcinoma and squamous cell carcinoma, whereas for SCLC it is dramatically low. In France, it was reported that in both sexes the proportion of adenocarcinoma patients significantly increased between 2000 and 2010, while that of squamous cell carcinoma and SCLC decreased [28]. Very similar patterns were observed in both national and regional studies in Switzerland [29, 30]. Difference in distribution of histologic

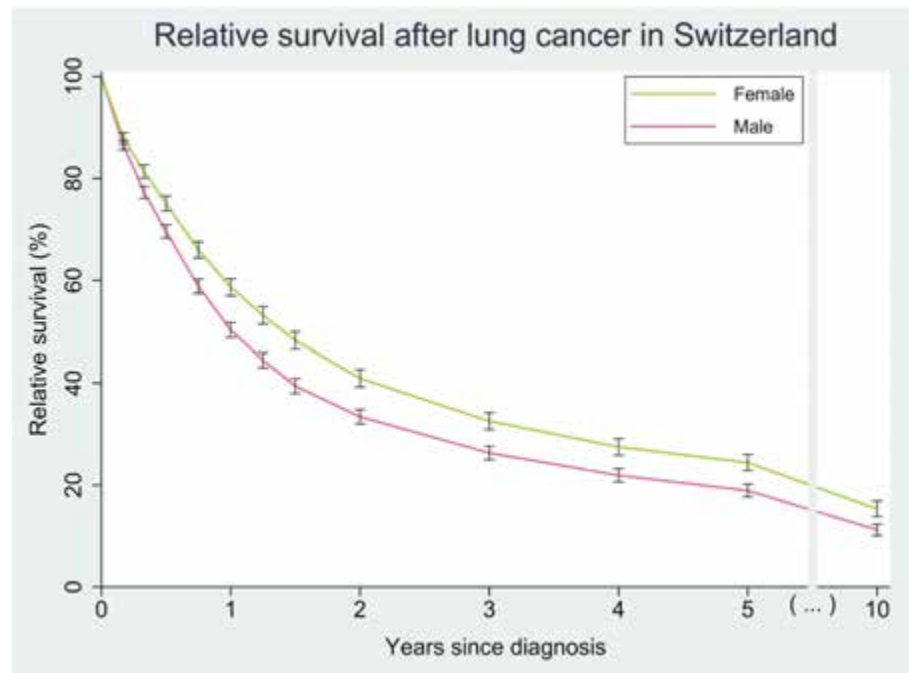


Fig. 1. Relative survival curves (age-standardized estimates) with 95% confidence intervals by sex for the follow-up period 2011-2015. Male and female lung cancer cases were pooled from seven Swiss cancer registries.

Years since diagnosis	Men						Women					
	1		5		10		1		5		10	
	RS	95% CI	RS	95% CI	RS	95% CI	RS	95% CI	RS	95% CI	RS	95% CI
<b>Histology</b>												
SCLC	39.7	[36.2, 43.2]	4.1	[2.6, 5.9]	3.0	[1.8, 4.9]	43.0	[39.0, 46.9]	5.3	[3.7, 7.3]	3.8	[2.4, 5.8]
NSCLC	51.3	[49.8, 52.9]	18.3	[17.1, 19.6]	10.8	[9.7, 12.0]	60.7	[58.9, 62.5]	24.7	[23.1, 26.4]	15.5	[13.9, 17.1]
<b>TNM stage</b>												
I	93.1	[90.4, 95.1]	66.1	[61.4, 70.4]	38.8	[33.6, 44.0]	97.9	[95.6, 99.0]	72.4	[67.3, 76.9]	50.2	[43.5, 56.5]
II	83.9	[79.5, 87.4]	39.6	[33.7, 45.5]	22.9	[17.2, 29.1]	90.0	[84.8, 93.4]	55.7	[47.4, 63.2]	38.2	[28.5, 47.8]
III	62.2	[58.9, 65.4]	16.5	[14.0, 19.3]	9.9	[7.7, 12.5]	70.1	[65.9, 73.8]	23.1	[19.4, 27.0]	12.6	[9.1, 16.7]
IV	27.4	[25.6, 29.3]	1.2	[0.9, 1.7]	0.5	[0.3, 0.9]	36.9	[34.6, 39.2]	3.0	[2.3, 3.9]	1.4	[0.8, 2.2]
Missing	48.2	[44.8, 51.5]	12.7	[10.6, 15.1]	7.9	[6.2, 9.9]	55.9	[52.1, 59.5]	20.0	[17.2, 22.9]	12.9	[10.5, 15.6]
<b>Age group</b>												
30-54	56.5	[52.0, 60.7]	20.0	[16.5, 23.8]	14.6	[11.6, 18.0]	68.3	[63.8, 72.5]	28.5	[24.3, 33.0]	21.6	[17.5, 25.9]
55-64	55.7	[52.9, 58.4]	20.2	[18.0, 22.6]	12.7	[10.8, 14.9]	63.7	[60.5, 66.7]	24.6	[21.8, 27.5]	16.0	[13.5, 18.8]
65-74	52.2	[49.9, 54.4]	16.9	[15.2, 18.8]	9.4	[7.9, 11.1]	59.4	[56.6, 62.1]	23.8	[21.2, 26.4]	14.1	[11.7, 16.7]
75+	37.6	[35.2, 40.1]	9.5	[8.0, 11.1]	4.0	[2.8, 5.5]	44.9	[41.5, 48.2]	11.8	[9.7, 14.2]	5.7	[3.9, 8.0]

Tab. 2. One-, five- and ten-year sex-specific relative survival estimates (in %) with 95% confidence intervals (95% CI), stratified by tumour histology, TNM stage and age at diagnosis. All estimates are age-standardized, except the crude, age-specific figures.



types may also partially explain different survival experiences for the two sexes. Genetic and hormonal factors have been associated with better prognosis of lung cancer among women [10]. Moreover, women seem to experience longer survival after both resection of early stage tumour and treatment for metastatic disease [10]. Finally, survival after lung cancer in non-smokers has been reported to be higher than that after lung cancer in smokers, and lung cancer not associated to smoking habits is much more frequent among women than among men [3, 31, 32].

SCLC is much less common, but far deadlier than NSCLC. It is an aggressive tumour of neuroendocrine origin with a rapid doubling time and tendency to spread early to other organs [9]. The five-year relative survival is lower than 5%, mainly because of the unfavourable stage distribution: in our analysis, 61% of NSCLC cases were diagnosed at stages III-IV, whereas SCLC stages III-IV were observed at diagnosis in 93% of the cases (data not shown). Regardless of histology, TNM stage at diagnosis is a very important prognostic factor for lung cancer, as also the majority of NSCLC cases are diagnosed at advanced stages. A patient diagnosed with malignant lung cancer can expect a five-year survival probability that ranges from 66-72% if the tumour is at stage I, to 1-3% if diagnosed at stage IV. Early diagnosis is therefore likely to dramatically improve survival following lung cancer. A recently published modelling study has evaluated the cost-effectiveness of a lung cancer screening program in Switzerland by using the results from two major screening trials. The main conclusions were that screening by low-dose CT scan (LDCT) may be feasible in Switzerland, and that in the most cost-effective scenario lung cancer mortality may be reduced by up to 15%, although the costs of the intervention would be considerable [33].

Survival varies less by age group than it does according to sex, histology and TNM stage at diagnosis. However, in both sexes it is noticeably lower among individuals aged 75 or more compared to younger individuals. The worse survival experience of older patients may be attributed to a greater prevalence of comorbidities interacting with lung cancer, as well as to a higher treatment toxicity [11, 12]. Tumour resection is often considered not feasible at higher ages, however as less invasive surgery options become available, more effective treatment possibilities will be accessible to the elderly [34].

One- and five-year survival are used as a standard for quantifying lung cancer prognosis, as historically lung cancer survival has been very low already after five years from diagnosis. However, as survival gradually improves it becomes necessary to characterise cancer prognosis over a longer period. Indeed, in this work we observed that ten-year age-standardized relative survival for 2011-2015 is as high (11-15%) as the five-year survival that was reported in Switzerland for the period 1995-1999 [13].

In summary, in 2011-2015 lung cancer survival in Switzerland was higher than that reported for previous periods, likely because of improved diagnosis and treatment, as well as because of the shift towards histologies with more favourable prognosis. A screening program was found to be potentially cost-effective in Switzerland, and the relevant stakeholders should evaluate its actual feasibility and affordability. Despite the improvements, lung cancer survival is still much lower than that of other cancer types, which underlines the importance of pursuing smoking cessation, as it is an effective preventive measure and even provides enhanced survival experience among individuals already diagnosed with lung cancer [35]. Finally, as the elderly have a poorer prognosis than the rest of the population and represent a large group of lung cancer survivors in Switzerland, it is essential to take into account their specific healthcare needs.

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